6 DIET AND DISEASE

In *1982* the *National Research Council*, a branch of the US National Academy of Sciences, issued provisional guidelines intended to reduce the risk of cancer related to food. The main recommendations were to lower fat intake from the current US average of 40% of total calories to 30%; to eat more fibre, fruit and vegetables; to increase consumption of complex carbohydrates (e.g. starch in potatoes and flours), and to decrease consumption of pickled, salted or smoked foods as well as simple carbohydrates (e.g. refined sugar). These recommendations led to a considerable amount of controversy, arising mainly from the fact that although the evidence on which the recommendations were based was highly suggestive, it was by no means definitive.

There are two major sources of evidence suggesting a role for dietary factors in cancer: epidemiological studies and laboratory experiments with rodents. Comparisons of cancer death rates among different national populations have provided important clues to the causation of cancer.

6.1 Food Intake in Animals

Laboratory workers have known for decades that tumour incidence in animals can be affected by gross nutritional manipulation *(e.g. Conybeare, 1980)*.

6.2 Dietary Studies in Humans

Interest in the relationship between diet and cancer in human beings has been stimulated by international studies in which large differences in cancer incidence rates have been found between countries *(Doll and Peto, 1981)*; for example, age-adjusted rates of breast and colon cancer in many areas of the world are less than one fifth of those in the United States.

One of the most informative between-country comparisons is between the United States and Japan. Both countries have similar levels of industrialisation and education, high medical standards and good statistics. Surprisingly, although the overall cancer rates are similar, the two countries yield mirror images when specific types of cancer are compared. For example, cancers of the breast, colon and prostate are common in the US but rare in Japan. Conversely, cancer of the stomach is common in Japan but rare in the US. One might answer that the differences are based on genetic differences between the two populations. That hypothesis is refuted by the data on migration from one country to another. They show that some of the worldwide variation in cancer rates can be attributed to environmental factors rather than genetic ones. For example, within two generations Japanese immigrants in Hawaii and California had breast-cancer rates approaching those of the Hawaiian white population and significantly higher than those of native Japanese. Conversely, gastric cancer rates became significantly lower among Japanese Hawaiians than among native Japanese.

Such shifts naturally focus attention on the possibility that differences in diet may be a factor. Another epidemiological clue came from the analysis of long-term trends in the incidence and mortality rates of cancer. The data show that in a given country the mortality rate for a particular cancer often varies with time. The changes may particularly be related to changes in the population's dietary habits. For example, in developing countries as much as 80% of total calories comes from cereals and grains, which consist of

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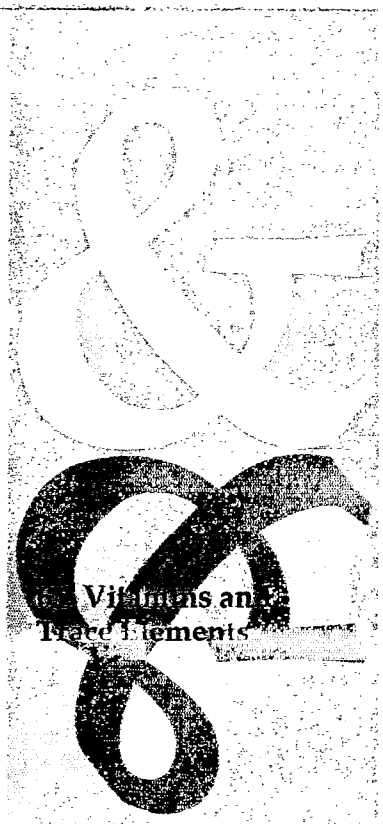

complex carbohydrates. With industrialisation and economic advance the caloric intake shifts towards fats derived from meat and vegetable oil, and the consumption of sugar (simple carbohydrate) also increases. As the changes have occurred, rising rates of breast and colon cancer (and of prostate cancer in certain countries) have been observed (see *Cohen, 1987*).

The central problem in interpreting human studies is that many factors other than dietary differences distinguish countries with a high incidence of cancer from those with a low incidence. For example, with a few notable exceptions such as Japan, countries with a low incidence of breast and colon cancer tend to be relatively undeveloped in economic terms. Therefore, any variable related to economic development can be similarly correlated with incidence of breast cancer.

By and large, work in this area has been related to the hypothesis that trace elements and vitamins may exert an 'anticancer' effect, in distinction to gross changes in diet which are thought to be causative factors in cancer (i.e. fibre deficiency or high fat intake).

Vitamin A

The interpretation of Vitamin A studies is complicated by the diversity of Vitamin A sources. Natural preformed Vitamin A (retinol) is found only in food from animal sources. Plants do not contain Vitamin A, but do contain compounds such as carotene which can be metabolised by animals and human beings to form retinol. Questionnaires employed in studies of Vitamin A and cancer have inquired primarily about plant rather than animal sources, so that these investigations really refer to the effects of carotene, rather than of preformed Vitamin A itself. A protective effect against lung cancer is currently the most strongly supported effect of vitamin A *(e.g. Wald et al, 1980; Willett & MacMahon, 1984)*.

Vitamin C

Evidence relating to the possibility that Vitamin C reduces the risk of cancer is somewhat equivocal, although ingestion of large quantities of Vitamin C has been reported to be beneficial in both the prevention of cancer and the treatment of established cancer *(Cameron et al, 1979)*.

Vitamin E

Compared even to Vitamin C, the epidemiological evidence for a possible protective effect of Vitamin E against cancer is small (see *Wald et al, 1987*). Nevertheless, since Vitamin E is an important intracellular antioxidant that reduces genetic mutations in some bacterial testing systems, it deserves, and will almost certainly receive, further study.

Selenium

Selenium is an essential trace element that has a key role in the activity of an enzyme that protects against oxidative tissue damage in cells. As oxidation is thought by some to be involved in cancer-producing processes, selenium levels are of considerable interest but have, until recently, not been studied as much as vitamins A, C and E. The current position on selenium is reviewed by *Willett & Stampfer (1988)*.

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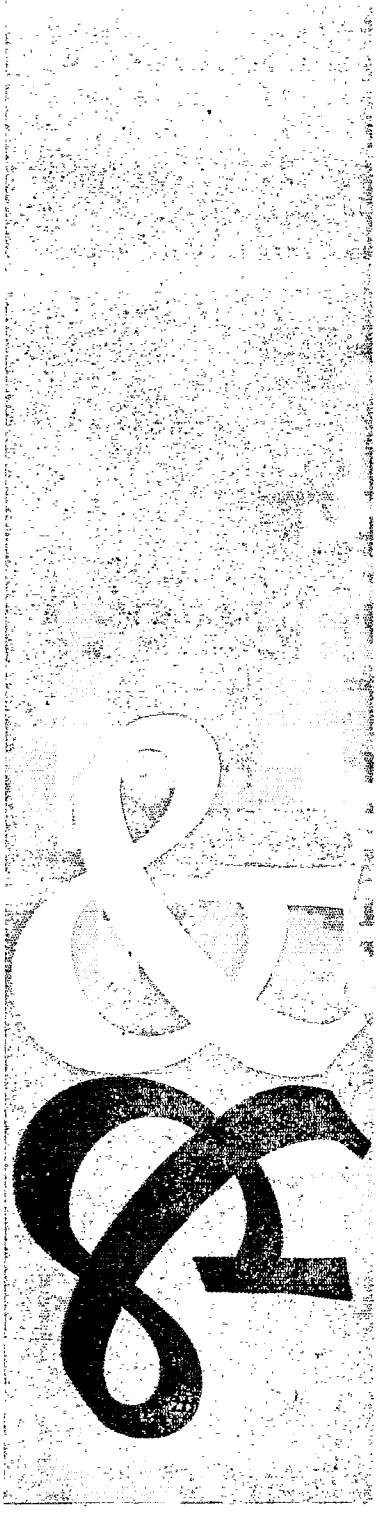
7 GENETICS, MOLECULAR BIOLOGY AND DISEASE

7.1 Cancer



It is probably not useful to think in terms of a single cause for cancer or even of cancer as a single disease. Spontaneously occurring cancer is probably most often a consequence of multiple factors ('risk factors') that interact over long periods of time. However, a significant body of scientists hold the view that cancer is primarily an impairment of cellular control mechanisms i.e. the mechanisms that control the growth and multiplication of cells. Cell growth mechanisms, like most functions in the body, are under genetic control i.e. there are certain genes in the cell whose function is to regulate the functioning of the cell. Occasionally, the controls that regulate cell multiplication and growth break down, and a cell begins to grow and divide even though the body has no need for further cells of its type. Ultimately, a mass called a tumour may be formed by this group of unwanted cells.

The genetic controls that regulate cell multiplication and growth can break down in a number of ways. For example:

Mutation

A mutation is a change in the chemical structure of a gene (the carriers of genetic information that regulate the functions of the body). This alteration can occur in a variety of different ways: for example, it can occur as a result of a mistake when cells grow and divide; alternatively, some chemicals (called 'mutagens') and other factors like ultra-violet light can change the chemical structure of a gene. In some cases this change may not be important at all; however, in particularly important genes and in parts of the chemical structure that are essential for the gene's functioning it is believed by many to be the first step towards the development of cancer. If a gene is altered significantly it may be unable to carry out its function of regulating cell activity and growth; as a result of this lack of control a tumour may develop.

Viruses

Some cancers are believed to be caused by viruses. These viruses carry genetic material which they insert into the cell. The cell treats this new genetic material as it would the body's own genes, and the instructions that are carried by the genetic virus can seriously interfere with the functioning of a cell e.g. by instructing the cell to make chemicals (proteins) which change normal cells into malignant cells.

Oncogenes

Oncogenes are genes that are present in the cells of the body, but that do not normally function i.e. they are 'switched off'. Under certain circumstances these genes can be activated e.g. by the occurrence of a mutation. These genes, when activated, can cause normal cells to turn into malignant cells and thereby may lead to the development of cancer. A number of human genes have been found to be oncogenes, and have been found to be present in many different types of cancer cells e.g. bladder, lung, breast, large intestine, neural tissue, leukaemias.

Chromosomal abnormalities

In some forms of cancer, there are much greater changes in the genetic material in that whole chromosomes (structures which contain genes: each

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human cell except sex cells has 46 chromosomes) can be missing, leading to a loss of genetic information and therefore a change in the instructions given to the cell by genes. Alternatively, single genes can be missing. Such a case has recently been found for lung cancer: *Kok et al (1988)* discovered that, in all cases of lung cancer studied, a particular gene on a particular chromosome was always missing. Although the function of this gene or its particular relevance to lung cancer is as yet unknown, it may be an indication that people with a particular genetic makeup may be more likely to develop a disease than those with a different genetic makeup. This is referred to as 'genetic predisposition' to a disease. Genetic abnormalities can be inherited from the parents or can be the result of 'accidents' during the lifetime of the individual.

Other Genetic Factors in Cancer

Idle and his co-workers (e.g. *Ayesh et al, 1984*) have suggested that another genetic factor may be relevant to predisposition to disease. When chemicals that are believed to be potential carcinogens enter the body, they are present in non-active forms. As a result of the body's attempt to change these chemicals into a form which is easy to get rid of, the non-active chemicals (procarcinogens) may be changed into active chemicals. These changes, known as metabolism, are carried out by specific chemicals in the body known as enzymes. The action of these enzymes is under genetic control. Two versions of one particular controlling gene exist: some of the population have an 'extensive metaboliser' gene that allows them to change procarcinogens into carcinogens very effectively. This group have a relative risk for developing lung cancer of 17 compared to the group who have the second version of the gene: 'poor metabolisers'. This group metabolises procarcinogens into carcinogens very ineffectively, and have a lower risk of developing lung cancer. This particular 'genetic predisposition' to develop lung cancer is independent of exposure to other factors. There have also been a number of other suggestions that particular subgroups of the population may be susceptible to develop particular diseases by virtue of their genetic makeup; however, few of the others have sound experimental backing.

7.2 Respiratory Disease

Some individuals inherit a gene which results in them having only very small quantities of a naturally-present chemical that protects the lung from decreasing in elasticity. As a result of the deficiency of this chemical, emphysema can occur. 5% of all emphysema patients have this deficiency (called 'alpha$_1$-antitrypsin deficiency').

7.3 Heart Disease

Although little is known about genetic factors in heart disease, it has been suggested that there might be a genetic component to atherosclerosis (a disorder of the large arteries). *Simons et al (1984)* suggested that heart disease also clusters in families, and that this might be explained by genetically-controlled differences in levels of compounds such as cholesterol.

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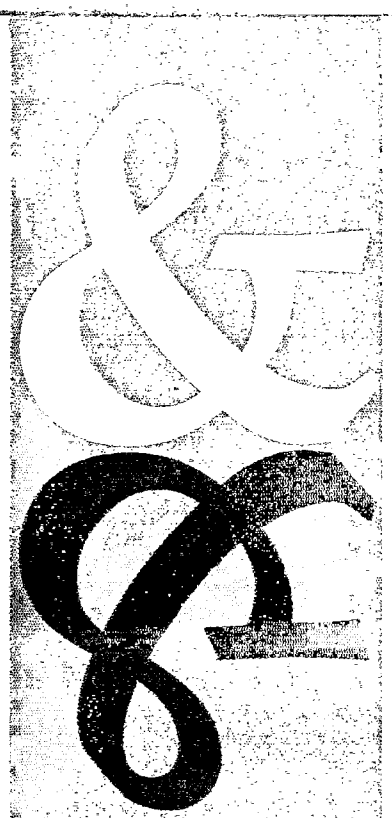

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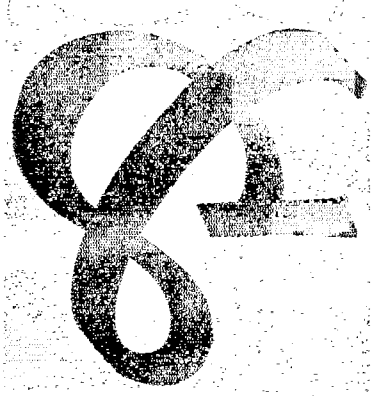

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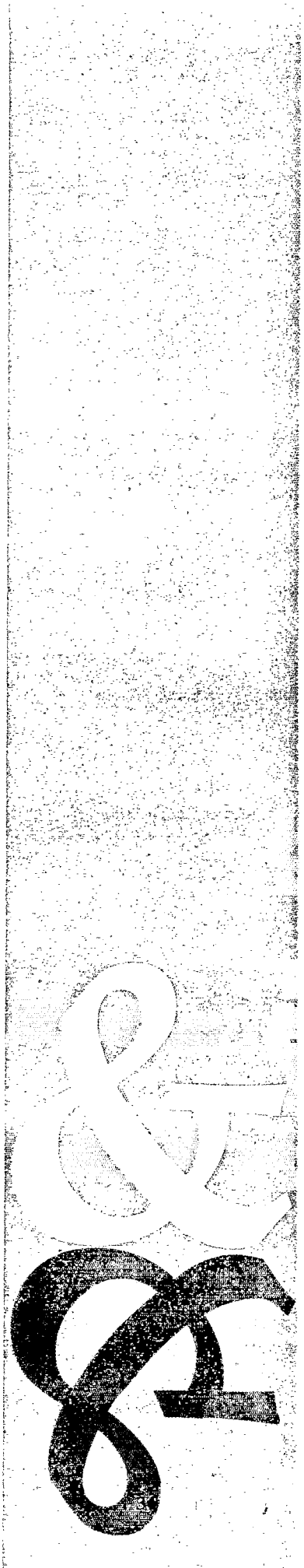

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